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10/521,522	08/15/2005	Andrew Powell	4033.3000 US	2122

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EXAMINER	
WESSENDORF, TERESA D	
ART UNIT	**PAPER NUMBER**
1639	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,522	POWELL ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *16-22,24 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicants' election with traverse of Group VII, the species of "step K" is acknowledged. The traversal is on the ground(s) that Group III is wholly embraced by Group II as a process which has "at least two modifications" necessarily embraces all processes that have at least three modifications. Obviously, Groups I and II are wholly embraced within Group I, which is directed to a method for the production of a library of heparin sulphate derivatives broadly. Thus, the special technical feature of Group III, a process with at least three modifications "is recited in" all three groups. The fact that Group II embraces some processes not also embraced within Group III (i.e., processes with two and only two modifications), does not justify a finding that the inventions lack unity of invention under the PCT. With respect to the claims that are assigned to each group, it is respectfully pointed out that Claims 2-5 (assigned only to Group I) also embrace processes which fall within the scope of Groups II and III. That is, Claims 4 and 5 make clear in the use of the phrase "at least one" that a plurality of chemical modifications (including two, three or more) are literally contemplated and embraced. Applicants also traversed the restriction between Groups I-III,

discussed above, and IV-VI. Group I wholly embraces each of Groups IV- VI. Thus, the special technical feature of Group IV is within Group I and the Examiner's reasoning for the restriction is technically flawed. Group II wholly embraces Groups V and VI while Group III embraces Group VI. Likewise, Group V embraces Group VI and Group IV embraces Groups V and VI. In other words, Group I is generic to all of Groups II-VI; Group II is generic to Groups III, V and VI and at least Claims 9-11 of Group IV; Group III is generic to Groups V and VI and at least Claims 10-11 of Group IV; Group IV is generic to Groups V and VI; and Group V is generic to Group VI. The restriction, at least as articulated, is actually a restriction between each genus and the next narrower or preferred subgenus or embodiment. It is not seen how the Examiner can rely upon Rule 13 of the PCT under the guidelines set forth in the MPEP in this situation. It is typical claiming practice to add dependent claims to recite one or more preferred embodiments of the claim above it. However, it is highly unusual to restrict between such claims. Turning to Groups VII and VIII, again, as is apparent from the fact that Claim 15 is a dependent claim of Claim 1, and Claim 16 requires that the process of Claim 1 be conducted, the inventions of these groups are also embraced by the invention of Group I. Indeed, the processes of Groups VII and VIII can be

practiced in combination with the processes of each and every one of Groups I-VI. Thus, for the reasons set forth above with respect to the restrictions between and among Groups I-VI, the restriction between and among Groups I-VIII is improper.

In view of applicants' arguments and upon reconsideration of the restriction requirement, the restriction has been revised. Groups I-VI will be examined with the elected group VII. However, group VIII, which contains the step of screening, as stated by applicants "to identify compounds with optimized properties" is withdrawn from further consideration. The elected groups are drawn to method of making, not to a method of screening a library especially in an array.

The requirement is still deemed proper and is therefore made FINAL.

Applicants state that while the species of "step K," has been elected it is to be understood that the elected process includes processes that perform, in addition to step K, other steps. That is, nothing within this election should be construed as an acquiescence that the claimed process consists of step K. The elected claims are directed to processes which comprise step K. Thus, it is Applicants' belief that the elected species will include processes which combine step K with one or two or more additional complete or partial modifications, such as a

modification to the amino functions of glucosamine (e.g., Claims 5-7), or steps A and K or B and K (e.g. claim 8, 10 or 11),for example. It is requested that, in the event that the claimed and elected processes, employing step K, are found to be patentable, that the search and examination be expanded to the generic invention.

Claims 16-22 and 24-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement.

Status of Claims

Claims 1-25 are pending

Claims 16-22 and 24-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention,

Claims 1-15 and 23 are under examination.

Specification

The abstract of the disclosure is objected to because it uses the PCT abstract, which is not on a separate sheet. Correction is required. See MPEP § 608.01(b).

The disclosure is objected to because of the following informalities: at page 10, line 16 "(1_," is an incomplete

sentence. Spelling errors at e.g., page 40, line 16 of "astrong". Applicants are requested to check for other errors e.g., typographical since they are too numerous to mention specifically.

Appropriate correction is required.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors (typographical, grammatical and idiomatic). Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 1 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claimed method of producing a library of heparin sulfate derivates comprising the chemical modification steps of at least one steps selected from A-O reads on the natural biosynthesis of heparan sulfate(HS).The biosynthesis involves the formation of a nonsulfated precursor polysaccharide, which

subsequently undergoes a series of polymer-modification reactions e.g., desulfation.

(See www.med.unibs.it/airc/hspgs.html).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-15 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claim 1 is indefinite for failing to recite positive process steps by which the library is made by combining at least one of the chemical modification steps of A-O.

2. Non-sequitur for "the heparan sulfate starting material" in claim 3.

3. The use of parenthetical statements in e.g., claim 15 is improper as every feature or compound recited in a claim becomes a part of the overall subject matter. By placing terms in parenthesis renders the claim ambiguous as to whether or not said statement should be disregarded. Also, it is unclear to what conditions the steps can be jointly or separately done.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-15 are rejected under 35 U.S.C. 102(a) as being anticipated by Wu et al (The FASEB Journal, 4/2002).

Wu et discloses throughout the published article at e.g., page 539, abstract a method of making a heparin sulfate derivative comprising of 3-O, 6-O sulfates and the minimal length of oligosaccharide antithrombin iii(at-iii) binding. The binding sites for AT-III is regenerated on completely desulfated N-resulfated heparin and revealed the critical modification enzymes. The method could be used to identify critical functional groups on HS, and to generate HS library.

Wu et al further disclose at e.g., col. 2, page 539:

> HS is initially synthesized in the Golgi apparatus as a nonsulfated copolymer attached to HS proteoglycan core proteins by sequential addition of D-glucuronic acid alternating with N-acetyl D-glucosamine. This is followed by various modification steps including N-deacylation and

> N-sulfation of glucosamine, epimerization of GlcA to L-iduronic acid, S-O sulfation of uronic acid and 6-O sulfation and 3-O sulfation of glucosamine. All steps are catalyzed by different enzymes and the process is selective as to the position and number of modifications in a chain leading to extensive sequence diversity.
>
> Wu also discloses at e.g., page 540, col. 1 and col. 2 a method combined with in vitro modification and gel mobility shift assay (GMSA) to reveal the structural features of heparin oligosaccharide, which recognized and activates AT-III.

Wu discloses at the RESULTS section the method of making a library with the interaction between a pentasaccharide and AT-III wherein the starting pentasaccharide lacks a 3-O sulfation and a 6-O sulfation. The modified pentasaccharide showed binding for AT-III of 6-O. At page 542, col. 2, first complete paragraph up to page 543, Wu discloses that since the most critical modifications for AT-III binding are 3-O and 6-O sulfations, reconstitution at AT-III binding sites on completely desulfated and N-resulfated heparin sulfate (DSNS) is made by addition of 3-O and 6-O sulfates to the chain (which reads on claim 15 steps of forming a library based on the function of a modified HS). DSNS was first modified with different combinations of sulfatransferases. The modified chain strongly bound to AT-III and further addition of 2-O did not change the binding significantly. This proved it is possible to generate HS

libraries and reconstitute protein binding sites on DSNS chain by in vitro modification.

Accordingly, the broad claimed process of claim 1, which recites broadly only the combinations of the different combinations without a single process step is fully met by the specific process steps of Wu using specific combinations of e.g., desulfation and re-sulfation. Also, the broad claimed process of claim 15 which recites creating a further library from the first library of the different combinations is met by Wu, as discussed above.

Claims 1-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Ben-Artzi (6190875).

Ben Artzi discloses throughout the disclosure at e.g., col. 4, lines 43-57:

> A "combinatorial" synthesis of a diverse set of molecules in which several components predicted to be associated with the desired biological activity are systematically varied (reads on claim 1 and claim 15).

Ben-artzi further discloses in the Examples at e.g., col. 17, line 43 up to col. 18, line 25:

> … Chemically modified non-anticoagulant species of heparin were prepared from native heparin and heparin fragment….. Briefly, the pyridinium salt of heparin and heparin fragment underwent complete N-desulfation……Total desulfation of N and O sulfate groups was obtained by exhaustive desulfation…… The N-desulfated heparin fragment was N-acetylated……. or N-resulfated with sulfur trioxide trimethylamine complex, as described (20). An O-desulfated, N-acetylated heparin fragment was obtained by O-desulfating an N-acetylated heparin fragment as described (20, 22).(Reads on claim 1). Intact heparin was chemically modified by the same procedures. These modified heparins exhibited <5% of the anticoagulant activity of

heparin (23). (Reads on claim 15.) See further the detailed description in the Examples starting at col. 15, Example 1.

Claims 1-15 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Kariya et al (The Jrnl. of Biological Chemistry) or Baumann et al (Carbohydrate Research) or Ungarelli t al (5405949).

Kariya throughout the published article discloses at e.g., page 25949 col. 2:

Solvolysis of heparin affords complete removal of N-sulfate groups from GlcN residues, removal of a substantial part of 2-O-sulfate groups from iduronic acid(Id-oUA) residues, and incomplete removal of 6-O-sulfate groups from GlcN residues, which occur even under the most optimized conditions (35). Accordingly, the heparin derivative prepared by the subsequent N-resulfation contains significantly reduced amounts of 2-O-sulfate groups of IdoUA residues…

Baumann et al at discloses specific process steps of making a library of HS by combining the different specific steps at e.g., page 383, col. 1, including the Table, up to page 387, col. 2.

The broad claimed library of e.g., claim 1, read in the light of the specification defining a library as containing at least two of the modifications is fully met by the specific process steps of Kariya or Baumann. Claim 15 is also met by the process of Kariya or Baumann. Each of these references discloses that a modified product is further

modified by an additional modification step of e.g., partial or complete desulfation. The first modified product is determined by its function e.g., in vitro promotion of A31 fibroblast proliferation. (See each of the abstract).

Ungarelli discloses throughout the patent at e.g., col. 4, line 60 up col. 8 a process of producing a library with the structural formula as shown. The formula of Ungarelli which contains different substituents for each of the variables e.g., R and Z reads on the claimed library. These variables define the claimed modifications of e.g., sulfation, de-sulfation and so on. Note that N3 without the sulfur group indicates the N has been desulfated. See further the Examples and claims.

Claims 1-15 are rejected under 35 U.S.C. 102(b) as being anticipated by any one of den Born(The Jrnl. of Biological Chemistry, 1995) or Maccarana et al (The Jrnl. of Biological Chemistry, 1993) or Petitou et al (Eur. J. Biochem.).

Each of these references, throughout each of the published article, discloses a method of making a library by modifying heparin sulfate by the process of desulfation, resulfation and 0-desulfation, partial or complete.

De Born discloses the method of combining the different claimed modifications at e.g., page 31303, col. 1, the abstract.

See Maccarana et al's disclosure at e.g., page 23898, Experimental Procedures and Fig. 7, page 23903.

See Petitou at e.g., page 637, Material and methods section.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-15 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one of Ben-Artzi et al or Wu or de Born or Maccarana or Petitou in view of Kariya et al. Each of Ben-artzi, Wu, deBorn, Maccarana and Petitou (hereinafter the primary references) are discussed above. Each of these references does not teach complete de N-sulfation in glucosamine. However, Kariya throughout the article discloses at e.g., page 25949 col. 2:

> Solvolysis of heparin affords complete removal of N-sulfate groups from GlcN residues, removal of a substantial part of 2-O-sulfate groups from iduronic acid(Id-oUA) residues, and incomplete removal of 6-O-sulfate groups from GlcN residues, which occur even under the most optimized conditions (35). Accordingly, the heparin derivative prepared by the subsequent N-resulfation contains significantly reduced amounts of 2-O-sulfate groups of IdoUA residues…

It would have been obvious to one having ordinary skill in the art at the time the invention was made to make a library of the known derivatives of heparin sulfate as taught by each of Ben-artzi, Wu de Born or Maccarana or Petitou with complete N-sulfate removal in the GlcN residues as taught by Kariya. Kariya teaches said N de-sulfation by solvolysis occur under the most optimized conditions. N-desulfation of glucosamine in the method of any one of the above cited primary references would be expected to produce a predictable result. N-modification has been known or used either singly or in combination with the other modifications known in the art. N-desulfation of glucosamine is known in the art as one of the modifications that heparan sulfate undergoes even in its biosynthesis. One having ordinary skill in the art would have been motivated to employ N-desulfation step to obtain a library with an optimized result. One would expect that N-

desulfation in combination with the other modifications as taught in anyone of the primary references would yield a more diverse library. Ben-artzi teaches that the combinatorial library provides the advantage for screening for desired biologically active compounds when all the components comprising the library are known in advance.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571) 272-0765. The fax phone number for the organization where this application or proceeding is assigned is 571 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

tdw
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